Daratumumab-Based Maintenance in Patients with Relapsed Multiple Myeloma after Salvage Autologous Stem Cell Transplantation

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Principal Investigator: Muzaffar H. Qazilbash, MD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0423 Houston, TX 77030
Telephone: 713.792.2466
Fax: 713.794.4902
mqazilba@mdanderson.org

Co-Chair: Krina Patel, MD[1]

Collaborators: Behrang Amini, MD, PhD[2]
Fleur M. Aung[3]
Qaiser Bashir, MD[4]
Hans C. Lee, MD[1]
Katy Rezvani, MD, PhD[4]
Dawen Sui, MS[5]
Guilin Tang, MD, PhD[6]

[1] The University of Texas MD Anderson Cancer Center, Lymphoma/Myeloma Department
[2] The University of Texas MD Anderson Cancer Center, Musculoskeletal Imaging Department
[3] The University of Texas MD Anderson Cancer Center, Laboratory Medicine Department
[4] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[5] The University of Texas MD Anderson Cancer Center, Biostatistics Department
[6] The University of Texas MD Anderson Cancer Center, Department of Hematopathology

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1.0 Objectives

1.1 Primary Objective

To estimate the complete remission rate (CRR) by the International Myeloma Working Group (IMWG) criteria within 9 months post salvage auto-transplant with subcutaneous daratumumab and hyaluronidase-fihj plus pomalidomide maintenance therapy starting approximately 3 months post salvage auto-transplant in patients with relapsed myeloma.

1.2 Secondary Objective

To evaluate progression-free survival (PFS).

1.3 Exploratory Objective

To discover the impact of daratumumab and hyaluronidase-fihj plus pomalidomide on graft function and immune reconstitution.

2.0 Background

2.1 Overview of Disease/Maintenance Therapy post salvage ASCT

Treatment for multiple myeloma has changed significantly over the past decade. Induction therapy followed by upfront autologous stem cell transplant (ASCT) with melphalan 200 mg/m2 has shown significantly improved progression free survival and quality of life for patients with newly diagnosed multiple myeloma (MM).

Maintenance Therapy:

Furthermore, multiple randomized phase III trials have demonstrated significantly improved PFS and OS with the use of continued lenalidomide maintenance therapy post initial ASCT. However, despite these substantial improvements in therapy, the majority of patients will relapse 3-4 years later (1-7).

Salvage ASCT:

Due to earlier diagnoses and improved therapies, MM patients are living significantly longer and many are eligible for second ASCT that can yield a meaningful duration of remission. On the other hand, other patients may not

undergo ASCT in first remission, either due to aggressive disease which may relapse during 1st line induction therapy (including an IMID) or due to preference. Multiple studies have been conducted evaluating salvage ASCT and all demonstrated chemosensitivity and duration of remission after first ASCT were the most important prognostic factors for subsequent long-term disease control (8-17). For patients undergoing salvage ASCT, either as a second transplant or as a first transplant with previous relapse to induction therapy, no standard maintenance therapy has been established post transplant. In a recent study evaluating the addition of lenalidomide to melphalan conditioning for salvage transplant, complete remission rates in both groups (first ASCT after relapsed disease or second ASCT) is similar at 28%, with time for best response of 16-732 days (18).

Maintenance with Daratumumab and Pomalidomide post salvage ASCT:

IMIDs and proteasome inhibitors have been used post salvage ASCT as maintenance treatment, however cytopenias, toxicities, and resistance due to previous exposure to these drugs, decrease their applicability. The newly FDA approved monoclonal antibody daratumumab has established efficacy as a single agent in relapsed and refractory disease, however is not FDA approved as a maintenance option post autologous stem cell transplant. It is an IgG1 kappa human monoclonal antibody directed against CD38. It induces apoptosis directly through Fc mediated cross linking and immune mediated tumor lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity and antibody dependent cellular phagocytosis. Thus its potential role as maintenance therapy post salvage transplant is promising and worthy of investigation.

Daratumumab was approved by the FDA in November 2015 for IV infusion. More recently, in May 2020, FDA approved its subcutaneous formulation, daratumumab/hyaluronidase-fihj. Its advantages include a fixed-dose formulation, short administration time of 3-5 minutes, which is significantly shorter than the currently used IV formulation that is given over hours, and a significant reduction in infusion-related reactions. In the Phase 3 COLUMBA study (19) supporting the approval, daratumumab and hyaluronidase-fihj demonstrated a consistent overall response rate (ORR) and pharmacokinetics and a similar safety profile compared with intravenous daratumumab in patients with relapsed or refractory multiple myeloma. In addition, there was a nearly two-thirds reduction in systemic infusion-related reactions with daratumumab and hyaluronidase-fihj compared to intravenous daratumumab (13 percent vs. 34 percent, respectively).

Pomalidomide is the third-generation immunomodulatory drug (IMiD) that has been approved by the FDA in June 2017 for use in relapsed/refractory multiple myeloma in combination with daratumumab IV based on the results of

EQUULUS trial (20). As most of the myeloma patients eligible for salvage ASCT have been exposed to daratumumab, and are refractory to the 2nd generation IMiD, lenalidomide, we hypothesize that a combination of daratumumab and hyaluronidase-fihj plus pomalidomide will improve the patient accrual, and the disease control.

2.2 Daratumumab

Summary of Relevant Clinical Experience

Several phase I /II and II studies (19-21) in relapsed MM patients (4-5 median prior lines of therapy) with daratumumab as monotherapy have been completed. The phase 1 part of the GEN501 trial demonstrated the 16 mg/kg dose as most efficacious and no dose limiting toxicity was observed at any dose level; part 2 revealed an overall response rate of 36% (at least a partial response) and PFS of 5.6 months with the dose of 16 mg/kg. The SIRIUS phase II study similarly demonstrated ORR of 29% and PFS of 3.7 months. Combination therapy with daratumumab, lenalidomide and dexamethasone in a phase I/II trial (GEN503) in relapsed refractory patients with a prior median of 2 lines of therapy, demonstrated an ORR of 100%, and 18 month PFS of 72% (22).

3.0 Background Drug Information

3.1 Daratumumab Preparation – Subcutaneous

Daratumumab and hyaluronidase-fihj will be provided as a fixed-dose (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

3.1.1 Daratumumab Administration – Subcutaneous

[Daratumumab should be given according to product information: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf]

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 – 5 minutes in the abdominal subcutaneous tissues in the left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Reasons for continued observation on subsequent daratumumab injection may include but are not limited to the following: subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 < 480% at screening or developed FEV1 < 80% during the study without any medical history), subjects with injection related reaction (IRR) with the first injection of

study drug, subject with decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

3.1.2 Dara-SC Dosing:

Table 1: Dara-SC dosing schedule (whether in combination or monotherapy)

Weeks	**Schedule**
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24[a]	Every two weeks (total of 8 doses)
Week 25 and onward until PD[b]	Every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-4-week dosing schedule is given at Week 25

All daratumumab administrations will be in an outpatient setting. Subjects will receive pre-injection medications and post-injection medication as outlined in Sections 3.1.3 and 3.1.4 respectively.

Vital signs should be monitored extensively on Cycle 1 Day 1 before, and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

If an IRR develops, then the injection should be temporarily interrupted or slowed downIn the event of a life-threatening injection related reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab and hyaluronidase-fihj should be discontinued and no additional daratumumab and hyaluronidase-fihj should be administered to the participant. See Section 3.1.5 for instructions on the management of injection related reactions and local ISRs.

3.1.3 Guidelines for Prevention and Management of Injection Reactions:

All participants will receive the following medications 1 to 3 hours prior to each study drug administration:

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine: diphenhydramine 25-50 mg IV or PO or equivalent. Avoid IV use of promethazine.
    - After Cycle 6, if a participant has not developed an injection-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.

- Administer 20 mg dexamethasone (or equivalent) prior to every daratumumab injection. When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on daratumumab injection days.
- Dexamethasone is given orally or intravenously prior to the first daratumumab injection and oral administration may be considered prior to subsequent injection.

- If the subject does not experience a major systemic administration-related reaction after the first 3 doses, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).

Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional in Cycle 1 Day 1 and can be administered up to 24 hours before injection as per investigator discretion.
If necessary, all PO pre-infusion medications may be administered out of the clinic on the day of the injection, provided they are taken within 3 hours before the infusion.

3.1.4 Post-dose Medication:

Administer post-injection medication to reduce the risk of delayed injection related reactions as follows:

- Consider administering low-dose methylprednisolone (≤ 20 mg) or equivalent, the day after the injection. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the injection, additional post-injection steroids are not required, but may be considered by the investigator.
- For participants with a higher risk of respiratory complications (e.g. participants with mild asthma or participants with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history) the following post-injection medication should be considered:
  - Antihistamine (diphenhydramine or equivalent)
  - Leukotriene inhibitor (montelukast or equivalent)
  - Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
  - Control medications for lung disease (e.g. inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for participants with COPD)
- In addition, these at-risk participants may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If participants are hospitalized, then an improvement in FEV1 should be performed and documented prior to discharge. If these participants are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all injection. If the participant has not experienced a significant

medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major injection-related reactions, then these post-injection medications may be waived after 4 doses at the investigator's discretion.

- Any post-injection medication will be administered after the injection has completed.

3.1.5 Management of injection-related Reactions and Local Injection- site Reactions of Daratumumab-SC injection-related reactions :

Injection-related reactions are systemic reactions related to daratumumab administration. Participants should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any injection related reactions, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple participants will be dosed at the same time. If an injection related reaction develops during daratumumab and hyaluronidase-fihj administration, then the administration should be temporarily interrupted. Participants who experience AEs during daratumumab and hyaluronidase-fihj administration must be treated for their symptoms. Participants should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. In the event of a life-threatening injection related reaction (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab and hyaluronidase-fihj should be discontinued.

Injection-related Reactions Grade 1 or Grade 2:

If the investigator assesses a Grade 1-2 injection related reaction to be related to administration of study intervention, then the daratumumab and hyaluronidase-fihj administration should be interrupted. When the participant's condition is stable, daratumumab and hyaluronidase-fihj administration may be restarted at the investigator's discretion. Refer to the USPI for further details regarding continuation of daratumumab and hyaluronidase-fihj administration.

If the participant experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic

therapy and does not resolve within 6 hours from onset, then the participant must be permanently discontinued from daratumumab and hyaluronidase-fihj treatment.

Injection-related Reactions Grade 3 or Higher:

For injection related reaction AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab and hyaluronidase-fihj administration must be stopped, and the participant must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab and hyaluronidase-fihj administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of daratumumab and hyaluronidase-fihj administration.

If the intensity of the AE returns to Grade 3 after restart of the daratumumab and hyaluronidase-fihj administration, then the participant must be permanently discontinued from daratumumab and hyaluronidase-fihj treatment.

For injection related reaction AEs that are Grade 4, the daratumumab and hyaluronidase-fihj administration must be stopped, and the participant permanently discontinued from daratumumab and hyaluronidase-fihj treatment.

Recurrent Injection-related Reactions:

If a Grade 3 injection related reaction (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab and hyaluronidase-fihj administration, the participant must be permanently discontinued from daratumumab and hyaluronidase-fihj treatment.

Injection Site Reactions (ISR):

In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

3.1.6 Blood Typing and Cross-matching Interference

Red cell and platelet transfusions will be required for some patients undergoing maintenance therapy post autologous stem cell transplantation. It has previously been reported that daratumumab binds to CD38 expressed on the surface of red blood cells. Although this additional activity may interfere with blood typing and cross-matching, no AEs related to hemolysis have been reported. In previous trials, patients had their blood types assessed before their first daratumumab infusion. They were also encouraged to carry a card indicating their blood type for the duration of the study. In the event of a positive Coombs

test, individual blood banks used a variety of mitigation methods to safely provide blood products. Blood banks were also made aware that this effect could persist for up to 6 months after cessation of daratumumab treatment.

3.1.7 Injection Reactions

Most biologics carry a risk of injection reactions that typically develop during or shortly after the injection. They vary from mild to potentially life threatening and are commonly associated with various signs and symptoms. The mechanisms by which monoclonal antibodies elicit injection reactions remain unclear.

- Monoclonal antibodies may interact with their molecular targets on circulating blood cells, tumor cells, or effector cells recruited to the tumor site (e.g., rituximab with CD20), thereby promoting the release of inflammatory cytokines.
- Injection reactions may have a hypersensitivity component in which the molecular structure of the drug or a component of the drug formulation is recognized as an antigen by the immune system. IgE mediated events are rare but possible.
- Non-immune mediated hypersensitivities are frequent following monoclonal or polyclonal antibody administration. These reactions resemble immune mediated reactions, but an immune mechanism is not detectable. The majority of these reactions imitate the clinical features of milder immune reactions (erythema, urticaria), but greater severity, even a lethal outcome are possible.

There is no difference between the clinical manifestations of the immune-mediated and non-immune mediated reactions. They both may involve the cutaneous, respiratory, gastrointestinal, or cardiovascular systems. The management of both types of reactions is the same.

In both monotherapy and combination clinical trials, the incidence of any grade infusion reactions was 46% with the first infusion, 2% with the second infusion and 4% with subsequent infusions. The incidence of infusion modification due to reactions was 41%. Severe grade 3 infusion reactions included bronchospasm, dyspnea, laryngeal and or pulmonary edema, hypoxia and hypertension. Less serious infusion reactions that occurred in greater than 5% patients were nasal congestion, cough, chills, throat irritation and vomiting.

When used as monotherapy in clinical trials with 156 patients with relapsed and refractory myeloma, the most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). These resulted in delay of treatment for 15% of patients. The below tables are from the United States Product Insert and

describe adverse reactions in >10% of patients who (1) received with SC Daratumumab, and (2) IV Daratumumab.

Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (package insert, Rev. 5/2020)

Adverse Reaction	DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)	
	All Grades (%)	Grades ≥3 (%)
Infections		
Upper respiratory tract infection[a]	39	0
Bronchitis	16	0
Pneumonia[b]	15	7[#]
Gastrointestinal disorders		
Constipation	37	0
Nausea	36	0
Diarrhea	33	3[#]
Vomiting	21	0
Abdominal pain[c]	13	0
General disorders and administration site conditions		
Fatigue[d]	36	3
Pyrexia	34	0
Edema peripheral[e]	13	1[#]
Nervous system disorders		
Peripheral sensory neuropathy	34	1[#]
Dizziness	10	0
Respiratory, thoracic and mediastinal disorders		
Cough[f]	24	0
Psychiatric disorders		
Insomnia	22	3[#]
Musculoskeletal and connective tissue disorders		
Back pain	21	3[#]
Musculoskeletal chest pain	12	0
Metabolism and nutrition disorders		
Decreased appetite	15	1[#]
Skin and subcutaneous tissue disorders		
Rash	13	0
Pruritus	12	0
Vascular disorders		
Hypertension	13	6[#]
Hypotension	10	3[#]

[a] Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.

[b] Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.

[c] Abdominal pain includes abdominal pain, and abdominal pain upper.

[d] Fatigue includes asthenia, and fatigue.

[e] Edema peripheral includes edema, edema peripheral, and peripheral swelling.

[f] Cough includes cough, and productive cough.

[#] Only grade 3 adverse reactions occurred.

Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone [a]	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	96	52
Decreased lymphocytes	93	84
Decreased platelets	93	42
Decreased neutrophils	88	49
Decreased hemoglobin	48	19

[a] Denominator is based on the safety population treated with D-VMP (N=67).

3.1.8 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the sponsor-investigator. The sponsor-investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and disposal of the drug will be maintained by the site. Accountability records will include drug receipt/destruction dates, quantities, lot numbers, expiration dates (if applicable), and corresponding registered patient numbers.

All material containing daratumumab will be treated and disposed of as hazardous waste in accordance with governing regulations.

3.1.9 Daratumumab Destruction

Study drug should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

3.2 Pomalidomide

Pomalidomide is a thalidomide analogue, which exerts an immunomodulatory, antiangiogenic, and antineoplastic effect by the inhibition of the proliferation and induction of apoptosis of hematopoietic tumor cells, and enhancement of T cell- and natural killer cell-mediated immunity and inhibition of pro-inflammatory cytokine production (e.g., TNF-alpha and IL-6) by monocytes. The cytotoxic and immunomodulatory effects of pomalidomide are mediated by targeting substrate proteins (including Aiolos and Ikaros) for ubiquitination and subsequent degradation. Pomalidomide is available as oral capsules in 1, 2, 3 and 4 mg doses.

Pomalidomide will be administered at 2 mg/day PO once daily on Days 1 to 21 during the 28-day cycle. Pomalidomide dose may be reduced, or the treatment schedule may be modified for the management of the study drug-related toxicities. Pomalidomide may be taken with water. Subjects should not break, chew, or open the capsules. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal).

Dose Modification Instructions for Pomalidomide for Hematologic Toxicities Toxicity	**Dose Modification**
Neutropenia • ANC <500 per mm^3 or Febrile neutropenia (fever more than or equal to 38.5°C and ANC <1,000 per mm^3) • ANC return to more than or equal to 500 per mm^3	• Interrupt pomalidomide treatment, follow CBC weekly. • Resume pomalidomide at 2 mg daily.
• For each subsequent drop <500 per mm^3 • Return to more than or equal to 500 per mm^3	• Interrupt pomalidomide treatment. • Resume pomalidomide at 1 mg less than the previous dose
Thrombocytopenia • Platelets <25,000 per mm^3 • Platelets return to >50,000 per mm^3	• Interrupt pomalidomide treatment, follow CBC weekly • Resume pomalidomide treatment at 2 mg daily
• For each subsequent drop <25,000 per mm^3 • Return to more than or equal to 50,000 per mm^3	• Interrupt pomalidomide treatment • Resume pomalidomide at 1 mg less than previous dose.

Pomalidomide Side Effects

Common (occurring in more than 20% of patients)

● swelling (arm/leg) ● fatigue ● nerve damage (possible numbness, pain, and/or loss of motor function) ● dizziness ● fever ● skin rash	● abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure) ● constipation	● nausea ● diarrhea ● loss of appetite ● low blood cell counts (red, white, platelet) ● weakness ● pain ● muscle spasms ● difficulty breathing

Pomalidomide may cause low blood cell counts (white blood cells, red blood cells, platelets).

- A low white blood cell count increases your risk of infection (such as viral or fungal pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.
- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.

Occasional (occurring in 3-20% of patients)

● headache ● anxiety ● confusion ● chills ● difficulty sleeping ● itching/dry skin ● increased sweating	● high blood sugar (possible diabetes) ● dehydration ● weight loss/gain ● vomiting ● tremors	● kidney failure ● nosebleed ● cough ● severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Frequency Unknown, but between 1-10%

● heart attack/failure ● low blood pressure (possible dizziness/fainting) ● mental status change ● depression	● walking/balance problems (possible falling) ● inflammation of the intestines ● mouth blisters/sores (possible difficulty swallowing) ● blood in the urine ● abnormal liver tests (possible liver damage, yellowing of the skin and/or eyes)	● broken bone(s) ● collapse of bones in the spine ● bacteria in the blood ● multiorgan failure

Rare but serious (occurring in fewer than 3% of patients)

● inability to urinate ● liver failure	● breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)	● allergic reaction

Pomalidomide may cause you to develop another type of cancer (such as acute myeloid leukemia, a type of blood cancer).

Pomalidomide may also cause blood-clotting events (such as deep vein thrombosis, blood clots in the lungs, heart attack, and stroke).

4.0 Patient Eligibility

4.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Patient must have had relapsed disease prior to transplant, or undergone previous ASCT, followed by relapse and at least a partial response to salvage therapy.
2. Eligible patients will be enrolled in the protocol no less than 60 days and must be initiated no longer than 180 (+/- 14) days post ASCT.
3. Male or female patients 18 years or older.

4. Patients must have an Eastern Cooperative Oncology Group (ECOG) status of 0 to 2.
5. Patients' clinical laboratory values and toxicity must be as specified below within 14 days before the first dose of the study drug:
   - Platelet count >= 50,000/mm^3
   - Absolute neutrophil count >= 1000/ mm^3 (no growth factors within 5 days)
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3 x ULN
   - Creatinine <= 2.5 mg/dL
   - Recovered (i.e., <= grade 2 toxicity) from the reversible effects of autologous stem cell transplant.
6. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care must be obtained, with the understanding that consent may be withdrawn by the subject at any time without any prejudice to future medical care.
7. Left ventricular ejection fraction >= 40%(at the patient's last recorded echocardiogram (this could refer to pretransplant ECHO. ECHO may be repeated if the PI considers a repeat ECHO) No uncontrolled arrhythmias.

4.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Major surgery within 14 days before the first dose of study drug.
2. Radiotherapy within 14 days before enrollment.
3. Non-secretory disease, plasma cell leukemia, or previous allogeneic transplant.
4. Known active central nervous system involvement.
5. Inability or unwillingness to comply with the drug administration requirements.
6. Female subject is pregnant or lactating.
7. Seropositive for human immunodeficiency virus (HIV).
8. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
9. Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

10. Patients with a known history of asthma or chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal.
11. Patients with moderate or severe persistent asthma within the past 2 years and currently uncontrolled asthma of any classification.
12. Infection requiring IV systemic antibiotic therapy within 7 days before C1D1 of therapy.
13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations.
14. Failure to have fully recovered (i.e., <= grade 2 toxicity) from the effects of prior chemotherapy regardless of the interval since last treatment.
15. Patient is refractory or resistant to daratumumab and pomalidomide.
16. Co-morbid systemic illnesses or other severe concurrent disease that, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
17. If patient was unable to tolerate daratumumab or pomalidomide in the past.

5.0 Treatment Plan

5.1 Overall Design and Plan of Study

This will be a single arm, open label phase II, single center study of maintenance therapy with daratumumab/hyaluronidase-fihj and pomalidomide post salvage ASCT in patients with multiple myeloma.

The total number of patients to be treated in this study is 56 evaluable patients.

Patients should complete 2 cycles of therapy to be evaluable. For patients who receive fewer than 2 cycles due to progressive disease will be considered evaluable. Patient who received < 2 cycles due to AEs will be inevaluable for efficacy (response). All the other analysis will be conducted using intention to treat dataset.

Patients will have standard restaging studies prior to initiation of therapy. Standard post transplant therapy per institutional guidelines will be unaltered including prophylactic antibiotics, vaccinations and restaging.

Each cycle will be defined as a 28 day cycle. Drug holidays and break in therapy including those due to holidays, physician discretion and drug delivery are allowed as needed.

5.2 Daratumumab 1800 mg/hyaluronidase-fihj 30,000 units will be given SC weekly for weeks 1-8, followed by every 2 weeks for weeks 9-24, and then every month for weeks 25 until progression. On day 1 of each cycle, doses may be held if clinically indicated (i.e., active infections) for up to 4 weeks. If longer than 4 weeks, the PI will

evaluate and determine if the patient can continue on trial or must be taken off study. After day 1 of each cycle, subsequent doses may be held/skipped if clinically indicated (i.e., active infections) per PI or treating physician's discretion.

If daratumumab administration does not commence within the specified window (Appendix A), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 28 days will result in permanent discontinuation of daratumumab. Subjects who miss >/= 3 consecutive planned doses of daratumumab for reasons other than toxicity will be withdrawn from treatment, unless, upon consultation with the sponsor and review of safety and efficacy, continuation is agreed upon.

Subjects will receive pre-injection medications and post-injection medication as outlined in Sections 3.1.3 and 3.1.4 respectively. See Section 3.1.5 for instructions on the management of IRR and local ISRs.

5.3 Pomalidomide will be given at 2 mg PO daily from day 1-21 in the 28-day cycle. On day 1 of each cycle, doses may be held if clinically indicated (i.e., active infections) for up to 4 weeks. If longer than 4 weeks, the PI will evaluate and determine if the patient can continue on trial or must be taken off study. After day 1 of each cycle, subsequent doses may be held/skipped if clinically indicated (i.e., active infections) per PI or treating physician's discretion.

Pomalidomide not administered between days 1-21 in the 28 days cycle will be considered a missed dose. Administration may resume after active infection is resolved per PI or treating physician discretion. See section 3.2 for further instructions on toxicity management.

5.4 Prophylaxis for herpes zoster reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting daratumumab and continue for 3 months following treatment.

5.5 Dose Delay

Before each cycle, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 (http://ctep.cancer.gov/reporting/ctc.html). Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. If multiple toxicities are noted, the dose delays are per PI discretion; refer to guidelines that address the most severe toxicity.

5.6 Criteria for beginning a subsequent treatment cycle

Treatment with daratumumab will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be >= 1,000/mm^3
- Platelet count must be >= 50,000/mm^3

In addition, all other toxicity considered to be related to treatment must have resolved to <= grade 1, to the patient's baseline values, or to a level considered acceptable by the physician (e.g., hypokalemia that can be managed by replacements) before a new cycle of treatment may begin.

5.7 Criteria for delaying a subsequent treatment cycle

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment or has any of the below toxicities, dosing should be delayed until recovery.

- Grade 4 hematologic toxicities
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
    - Grade 3 nausea that responds to antiemetic treatment within 7 days
    - Grade 3 vomiting that responds to antiemetic treatment within 7 days
    - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
    - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

The maximum delay before treatment should be discontinued is 6 weeks or at the discretion of the Principal Investigator.

5.8 Management of Clinical Event

5.8.1 Nausea and/or Vomiting

Standard anti-emetics, including 5-HT_3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

5.8.2 Diarrhea

Diarrhea should be managed according to clinical practice, including administration of antidiarrheal therapy once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment.

5.8.3 Thrombocytopenia

Thrombocytopenia has been reported with daratumumab. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been managed with platelet transfusions according to standard clinical practice.

5.8.4 Neutropenia

Neutropenia has been reported with daratumumab. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been managed with G-CSF according to standard clinical practice.

5.9 Concomitant Treatment

Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care shall be available to patients as necessary. Radiotherapy is permitted to palliate symptoms during maintenance therapy. The following are examples of those permitted during the study:

- Growth factors (e.g., granulocyte colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), recombinant erythropoietin).
- Red cell and platelet transfusions as clinically indicated
- Prophylactic antibiotics for pneumocystis (i.e., Bactrim) needed post ASCT
- Antiviral prophylaxis (i.e.,Valtrex) is recommended for all patients to prevent HSV or zoster
- Bisphosphonate therapy
- Medications for neuropathy as needed at the discretion of the investigator.

Prohibited Concurrent Therapy

Other anti-myeloma directed systemic therapy

5.10 Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation see Appendix A.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

5.11 Contraception Requirements

Animal reproduction studies have not been conducted. Monoclonal antibodies such as daratumumab, are known to cross the placenta. Based on the mechanism of action, daratumumab may cause myeloid or lymphoid cell depletion and decreased bone density in the fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner.

Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception.

5.12 Duration of Treatment and Patient Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Patients will continue indefinitely unless the following occur:

- Lack of clinical benefit
- Patient's request to withdraw from the study or refusal of further therapy
- Unacceptable toxicity
- Pregnancy
- Physicians discretion
- Disease progression.
- Completion of up to 36 Cycles of study therapy

6.0 Evaluation During Study

6.1 Treatment and Event Schedule (see Appendix A.)

6.2 Efficacy measurements

Patients will be staged once every 3 cycles +/- 7 days while on protocol. Efficacy evaluations will be based on changes in: myeloma protein measurements in serum and 24 hour urine; serum free light chain assay; bone marrow biopsy examination with NGF-based MRD testing at 6 months from the start of maintenance (+/- 2 weeks); as clinically indicated skeletal survey or other imaging as clinically indicated; and, extramedullary plasmacytoma evaluation as clinically indicated.

7.0 Statistical Considerations

7.1 Sample Size Justification

The primary endpoint of this study is progression-free survival (PFS). According to clinical trial #NCT01998971 (28), we expect that the median PFS without maintenance therapy is 12 months and the median PFS for the daratumumab-based maintenance therapy is expected to be 20 months. Given an accrual period of 36 months and a maximum follow-up time of 60 months, a sample size of 56 with the number of events of 42 will achieve the power of 0.91. The result is based on a two-sided test, a significance level of 0.05 with exponential assumption for survival time (29).

7.2 Futility and Toxicity Monitoring

The secondary endpoint is the complete remission rate (CRR). Remission will be evaluated 6 months after daratumumab and hyaluronidase-fihj plus pomalidomide maintenance therapy (approximately 9 months post ASCT). Complete remission is defined as achieving a negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow. In patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required. The futility and toxicity will be monitored during the study.

We desire that the CRR is at least 10%and the dose-limiting toxicity rate is no higher than 33%. Toxicity is defined as treatment-related unmanageable toxicities, including grade 3 non-hematologic effects or grade 4 hematologic effects, that require delay or termination of the treatment during cycle one. Futility and toxicity will be monitored by the Bayesian stopping boundaries calculated on the basis of beta-binomial distributions using the method of Thall, Simon, and Estey (30). Independence is assumed between CR and toxicity. Patients will be monitored in cohorts of size (8).

We will enroll a minimum of 16 patients before stopping. The following stopping rules and boundaries were developed using the Multc Lean application (version

2.1) from the MDACC Biostatistics department. The stopping rules are as follows:

Pr [θ_E < 0.10 | data] > 0.90

Pr [T_E> 0.33|data] > 0.95

Enrollment will be stopped early if there is > 90% probability that the CRR is < 10% or there is > 95% probability that the toxicity rate is higher than 33%. The notation θ_E denotes the marginal remission rate, assuming that θ_E follows a prior distribution of beta (0.2,1.8). TE denotes the toxicity rate, assuming that TE has a prior distribution of beta (0.66, 1.34). The corresponding stopping boundaries for futility monitoring are as follows: enrollment will be stopped early due to futility if (# of patients with remission) / (# patients evaluated) </= 0/16-24, 1/32, 2/40-48, or 3/56.

Stopping boundaries corresponding to this probability criterion for toxicity will terminate the trial if (# of patients with toxicity) / (# patients evaluated) >/= 9/16, 13/24, 16/32, 19/40, 22/48, or 25/56.

We will suspend accrual while waiting to assess patient outcomes.

The operating characteristics of these rules are shown in the table below.

	True Pr(Response)	True Pr (Tox)	Pr (Stop Early)	Average # treated
1	10%	15%	0.32	46.0
2	10%	33%	0.38	44.0
3	10%	40%	0.55	39.1
4	20%	25%	0.04	54.4
5	20%	33%	0.13	52.0
6	20%	40%	0.36	45.6
7	25%	20%	0.013	55.5
8	25%	33%	0.10	52.8
9	25%	40%	0.35	46.2
10	30%	20%	0.005	55.8
11	30%	33%	0.10	53.1
12	30%	45%	0.60	39.0
13	40%	20%	0.002	55.9
14	40%	33%	0.09	53.2
15	40%	45%	0.60	39.1

The dataset for efficacy will be based on evaluable patients while the dataset for safety includes all patients who receive the maintenance therapy and will be

evaluated as intention to treat (ITT). Based on the toxicity profile of daratumumab, we do not expect to have patients who receive fewer than 2 cycles due to AE's.

Patient who received < 2 cycles due to AEs will be inevaluable for efficacy (response). All the other analysis will be conducted using intention to treat dataset.

7.3 Analysis Plan

Patients' demographic, clinical characteristics, and safety data will be summarized using descriptive statistics such as mean, standard deviation, median, interquartile range, and frequency where appropriate.

Progression-free survival is defined as the interval from the date of initiation of maintenance therapy after salvage ASCT to the earlier of the first documentation of objective disease progression or death from any cause. Disease progression will be assessed using myeloma protein measurements in serum and 24 hour urine; serum free light chain assay; bone marrow biopsy examination with MGF-based MRD testing at 6 months (+/- 2 weeks) from the start of maintenance, and then yearly as indicated; skeletal survey or other imaging as clinically indicated; and, extramedullary plasmacytoma evaluation as clinically indicated. Progression is defined by the IMWG as a 25% increase from the lowest response value in any of the following: a) serum M protein with absolute increase >= 0.5 g/dL, b) urine M protein with absolute increase of at least 200 mg/24 hour, c) difference between involved and uninvolved FLC levels with absolute increase of at least 10 mg/dL (in patients without measurable serum or urine M protein), d) bone marrow plasma cell percentage with absolute percentage of at least 10% (in patients without measurable serum or urine M protein or FLC levels), e) new or definite increase in size of existing bone lesions or soft tissue plasmacytoma, f) development of hypercalcemia that can be attributed solely to myeloma. Data from surviving, non-progressing patients will be censored at the last time of follow-up. Progression-free survival will be summarized descriptively using the Kaplan-Meier method (including the median, 95% confidence interval, and survival curve). The proportion of patients alive and without disease progression at 6 months of daratumumab and hyaluronidase-fihj plus pomalidomide maintenance therapy will be summarized. The estimate will be accompanied by a two-sided exact 95% binomial confidence interval. In addition, a Cox regression analysis may be performed if demographic and clinical factors potentially affecting PFS are identified.

The associations between/among safety data, prognostic factors, and the response will be assessed using student t-test/Wilcoxon rank test, ANOVA/Kruskal-Wallis test, chi-squared test/Fisher's exact test, or Logistic regression model as appropriate. Complete remission rate will be estimated along with a 95% credible interval.

8.0 Reporting Requirements

Safety Measurements and Reporting

Before starting each cycle, patients will be evaluated for toxicity. Safety evaluations will be based on changes in physical examinations, ECOG Performance Status scores, clinical laboratory findings from pretreatment to the End-of-Treatment Visit, and on the observation or report of any AEs (including laboratory abnormalities reported as AEs) that occur from time of consent until 30 days after the last dose of study agent and those SAEs (including laboratory abnormalities reported as AEs) occurring after 30 days if considered related to daratumumab. The intensity (severity) of AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.

8.1 Overview

As the sponsor of the Study, the University of Texas MD Anderson Cancer Center (UTMDACC) and the Principal Investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

UTMDACC and the Principal Investigator will provide safety information to J&J on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

8.2 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events for J&J Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a

subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented dose of study drug within the study.

For the purposes of this study, the J&J medicinal product is:
DARZALEX™ (daratumumab) and
DARZALEX Faspro™ (daratumumab and hyaluronidase-fihj).

8.3 Definitions:

8.3.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

8.3.2 Adverse Events of Special Interest

Adverse events of special interest are events that J&J is actively monitoring as a result of a previously identified signal (even if non-serious).

- These adverse events are: Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- HBV Reactivation
- Other malignancies

Any Adverse Event of Special Interest that is to be reported to J&J should be recorded on a Serious Adverse Event Report Form and be reported to J&J within 24 hours of knowledge of the event.

8.3.3 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a J&J medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected J&J medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- J&J protocol ID

8.3.4 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g., abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

8.3.5 Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the

hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

8.4 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.
http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

http://www.janssenlabels.com/package-insert/product-monograph/prescribinginformation/DARZALEX+Faspro-pi.pd

For DARZALEX™ (daratumumab) and DARZALEX Faspro™, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

8.5 Special Reporting Situations

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product

- Inadvertent or accidental exposure to a J&J medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product
- Medication error involving a J&J medicinal product (with or without patient exposure to the J&J medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a J&J medicinal product

These safety events may not meet the definition of an adverse event; however, from a J&J perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to J&J within 24 hours of becoming aware of the event.

8.6 Pregnancy

All initial reports of pregnancy must be reported to J&J by the Principal Investigator within 24 hours of becoming aware of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the J&J medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported by the Principal Investigator within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.7 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. UTMDACC and the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g., to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at J&J request.

8.8 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for J&J Medicinal Products to J&J

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a J&J medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.

All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed-up in accordance with clinical practice.

8.8.1 SAEs, Adverse Events of Special Interest, and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

UTMDACC and the Principal Investigator will transmit all SAEs, Adverse Events of Special Interest, and special situations following exposure to a J&J product under study in an SAE form provided by J&J in accordance within the section titled, Transmission Methods, in English within 24-hours of becoming aware of the event(s).

In the event the study is blinded, the Principal Investigator will submit an unblinded SAE or pregnancy exposure report to J&J.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Principal Investigator, within 24 hours becoming aware, to J&J using the J&J Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- UTMDACC and the Principal Investigator is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant extraordinary (not including routine initial or follow-up ICSR submission) correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the J&J Product under study, are to be provided to J&J using a transmission method in Section 10 from this Exhibit within 24 hours of such report or correspondence being sent to applicable health authorities.

8.8.2 Non-Serious AEs

All non-serious adverse events should be reported to J&J according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

8.8.3 PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and J&J, and are mandated by regulatory agencies worldwide. J&J has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected for any reports of failure of expected pharmacological action (i.e., lack of

effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a J&J medicinal product under study must be reported to J&J by the Principal Investigator within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Principal Investigator must report the PQC to J&J according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by J&J.

8.9 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-J&J medicinal product under study, the Principal Investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

8.10 Transmission Methods

The following methods are acceptable for transmission of safety information to J&J:

- Electronically via J&J SECURE Email service (preferred) IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report 1-866-451-0371
  - Telephone (if fax is non-functional).

Please use the contact information and process information provided by J&J.

9.0. Data Management and Confidentiality

9.1 Data Collection and Management Responsibilities

Data Capture: Data will be entered in the MD Anderson institutionally approved database (s) Electronic Data Capture Tool, a CFR 21 Part 11 compliant system. All eligibility criteria must be documented prior to treatment initiation.

All data collected will be used only for research purposes by MDA and J&J. Identifiers (name, medical record number, date of birth, treatment diagnosis, imaging tests, follow-up and death) may be collected but will be replaced by study numbers in the analytic files. Patient identifiers will be confidentially collected and securely maintained on a password protected server located behind the institutional firewall. Access to identifiers will follow IRB and MDA information security rules and regulations. The master database file will be accessible only to the Principal Investigator, Financial Supporters, approved collaborators, and research staff designated on the delegation of authority log.

Accuracy of Data Collection: The MD Anderson Principal Investigator will be the final arbiter of response and toxicity, should a difference of opinion exist.

9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. J&J may receive PHI although such access to PHI is limited to the terms of the agreement defined in the contract. The contract allows for J&J to use the data for research purposes, not limited to this study only.

10.0 References

1. P. Singh, S.K. Kumar, B.R. LaPlant, *et al.* Lenalidomide maintenance therapy in multiple myeloma: a meta-analysis of randomized trials Blood, 122 (2013), p. 407
2. M. Attal, V. Lauwers-Cances, G. Marit, *et al.* Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med, 366 (2012), pp. 1782–1791
3. P.L. McCarthy, K. Owzar, C.C. Hofmeister, *et al.* Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med, 366 (2012), pp. 1770–1781
4. A. Palumbo, F. Cavallo, F. Gay, *et al.* Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med, 371 (2014), pp. 895–905
5. F. Gay, S. Oliva, M.T. Petrucci, *et al.* Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase III trial. Lancet Oncol, 16 (2015), pp. 1617–1629
6. M. Roussel, V. Lauwers-Cances, N. Robillard, *et al.* Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome J Clin Oncol, 32 (2014), pp. 2712–2717
7. M. Attal, V. Lauwers-Cances, C. Hulin, *et al.* Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial) Blood, 126 (2015), p. 391
8. Shah N, Ahmed F, Bashir Q, *et al.* Durable remission with salvage second auto-transplants in patients with multiple myeloma. Cancer. 2012;118:3549–3555.
9. Jimenez-Zepeda VH, Mikhael J, Winter A, *et al.* Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. Biol Blood Marrow Transplant. 2012;18:773–779.
10. Olin RL, Vogl DT, Porter DL, et al. Second auto-SC is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant. 2009;43:417–422.
11. Fenk R, Liese V, Neubauer F, *et al.* Predictive factors for successful salvage high- dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. Leuk Lymphoma. 2011;52:1455–1462.
12. Alvares CL, Davies FE, Horton C, et al. The role of second autografts in the management of myeloma at first relapse. Haematologica. 2006;91:141–142.
13. Silva Rondon C, Hassoun H, Chimento D, et al. Outcomes following salvage autologous stem cell transplant for multiple myeloma. Biol Blood Marrow Transplant. 2012;18:S254.
14. Gonzalvez WI, Gertz MA, Lacy MQ, et al. Second auto stem cell transplant for treatment of relapsed multiple myeloma. Bone Marrow Transplant. 2012;10:1–6.
15. Michaelis LC, Saad A, Zhong X, et al. Savage second hematopoietic cell transplantation in myeloma. Biol Blood Marrow Transplant. 2013;19:760–766.

16. Sellner L, Heiss C, Benner A, *et al.* Autologous retransplantation for patients with recurrent multiple myeloma. A single-center experience with 200 patients. Cancer. 2013;119:2438–2446.
17. Grövdal M, Nahi H, Gahrton G, *et al*. Autologous stem cell transplantation versus novel drugs or conventional chemotherapy for patients with relapsed multiple myeloma after previous ASCT. Bone Marrow Transplant. 2015;50:808–812.
18. Shah N, Thall P, Milton D, et al. Phase I/II Trial of Lenadliomide and High-Dose Melphalan with Autologous Stem Cell Transplantation for Relapsed Myeloma: Updated Results. Blood 2016, 128:2269.
19. Mateos MV, Nahi H, Legiec W, et al: Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol 7:e370-e380, 2020
20. Chari A, Suvannasankha A, Fay JW, et al: Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 130:974-981, 2017
21. Lokhorst HM, Plesner T, Laubach JP, *et al.* Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015; 373: 1207–1219.
22. Lonial S, Weiss BM, Usmani SZ, *et al.* Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. Lancet. 2016:1551-60.
23. Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood. 2016: 37-44.
24. Plesner T, Arkenau H, Gimsing P, *et al.* Phase I/II study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. Blood 2016.
25. Mantel N, Haenszel MW. Statistical aspects of thee analysis of data from retrospective studies of disease. J Nat Cancer Inst 2959; 22:719-48.
26. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis, 2nd Edition. New Jersey: John Wiley and Sons; 2011.
27. Qiu F, Stein CM, Elston RC; Tuberculosis Research Unit (TBRU). Joint Modeling of Longitudinal Data and Discrete-Time Survival Outcome. Stat Methods Med Res. 2016 Aug; 25(4):1512-26.
28. www.clinicaltrials.gov
29. Zhou Y., Yuan,Y., Lee J.J., Pan,H. (2019). Sample Size Calculation - Time-to-event Endpoint (V.2.1.0) [Computer software]. Retrieved from www.trialdesign.org.
30. Thall PF, Simon RM, and Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat med 1995 Feb 28;14(4):357-79.

Appendix A. Treatment and Event Schedule

	Study Visits										
Assessments	**Screening Phase**	**Treatment Phase (28-day cycles)**								**Follow-up Phase**	
		Cycles 1 & 2				**Cycles 3-6**		**Cycles 7+**	**EOT[a]**	**FUP[b]**	**Survival[b, i]**
Study Day:	**-28 to -1**	**1** (+/- 3 days)	**8** (+/- 3 days)	**15** (+/- 3 days)	**22** (+/- 3 days)	**1** (+/- 3 days)	**15** (+/- 3 days)	**1** (+/- 7 days)	**Post-Treatment 7 days** (+/- 7 days)	**Post-Treatment 90 (+3) days**	**q12wks** (+/- 7 days)
Informed consent	Subjects must sign the informed consent form before any study-specific procedures are performed										
Eligibility criteria	X										
Forced expiratory volume test (subjects with COPD or asthma)	X										
Demography/medical history	X										
Physical examination	X	X[o]				X[o]		X[o]	X[o]		
Weight		X				X		X			
ECOG performance status	X	X				X		X	X		
Blood pressure[c] and temperature	X	X	X	X	X	X	X	X	X		
Electrocardiogram and echocardiogram (The echocardiogram performed before stem cell transplant will be used until the PI considers a repeat echo before maintenance for medical reasons)	X										
Adverse event monitoring		Continuous from time of ICF until 30 days after last study treatment								Treatment-related SAEs	

Assessments	Study Visits										
	Screening Phase	Treatment Phase (28-day cycles)								Follow-up Phase	
		Cycles 1 & 2				Cycles 3-6		Cycles 7+	EOT[a]	FUP[b]	Survival[b,i]
Study Day:	**-28 to -1**	**1** (+/- 3 days)	**8** (+/- 3 days)	**15** (+/- 3 days)	**22** (+/- 3 days)	**1** (+/- 3 days)	**15** (+/- 3 days)	**1** (+/- 7 days)	**Post-Treatment 7 days** (+/- 7 days)	**Post-Treatment 90 (+3) days**	**q12wks** (+/- 7 days)
Dosing	**-28 to -1**										
Pre- and post-infusion medications[d]		X	X	X	X	X	X	X			
Daratumumab/hyaluronidase-fihi dosing (SQ)		X	X	X	X	X	X	X			
Pomalidomide 2 mg (PO)		Days 1 – 21 of each 28-day cycle									
Laboratory Assessments[e]	**-28 to -1**	**Cycles 1 & 2**				**Cycles 3-6**		**Cycles 7+**	**EOT[a]**	**FUP[b]**	**Survival[b,i]**
Blood type assessment and indirect antiglobulin results[m]	x										
Serum pregnancy test (women of childbearing potential only): (minimum requirement)	X[f]	See footnote f									
Biochemistry[g]	X	X				X		X	X	X	
Hematology[g]	X	X				X		X	X	X	
HBV Serology[p]	X										
HBV DNA Tests[p]	X										

	Study Visits									
Assessments	**Screening Phase**	**Treatment Phase (28-day cycles)**							**Follow-up Phase**	
		Cycles 1 & 2				**Cycles 3-6**		**Cycles 7+**	**EOT[a]**	**FUP[b]**	**Survival[b,i]**
Study Day:	**-28 to -1**	**1** (+/- 3 days)	**8** (+/- 3 days)	**15** (+/- 3 days)	**22** (+/- 3 days)	**1** (+/- 3 days)	**15** (+/- 3 days)	**1** (+/- 7 days)	**Post-Treatment 7 days** (+/- 7 days)	**Post-Treatment 90 (+3) days**	**q12wks** (+/- 7 days)
Disease Evaluations (Blood/Urine)[e]	**-14 to -1**	**Cycles 1 & 2**				**Cycles 3-6**		**Cycles 7+**	**EOT[a]**	**FUP[b]**	**Survival[b,i]**
Serum beta 2-microglobulin	X										
QIg (IgA, IgM, IgG, IgD, IgE)[n]	X	Every 2-3 cycles during treatment (+/-7 days)									
SPEP	X								X	X[b]	
UPEP (24-hr urine sample)	X								X	X[b]	
Serum calcium corrected for albumin	X								X	X[b]	
Serum FLC & serum/urine immunofixation	X								X	X	
Disease Evaluations (Other)	**-42 to -1**										
Bone marrow aspirate/biopsy and assessment of MRD	X	To confirm CR (including sCR)[j] Bone marrow biopsy examination with NGF-based MRD testing at 6 months from the start of maintenance (+/- 2 weeks) then as clinically indicated									
Skeletal survey	As clinically indicated	As clinically indicated									

Assessments	Study Visits										
	Screening Phase	Treatment Phase (28-day cycles)								Follow-up Phase	
		Cycles 1 & 2				Cycles 3-6		Cycles 7+	EOT[a]	FUP[b]	Survival[b,i]
Study Day:	**-28 to -1**	**1** (+/- 3 days)	**8** (+/- 3 days)	**15** (+/- 3 days)	**22** (+/- 3 days)	**1** (+/- 3 days)	**15** (+/- 3 days)	**1** (+/- 7 days)	**Post-Treatment 7 days** (+/- 7 days)	**Post- Treatment 90 (+3) days**	**q12wks** (+/- 7 days)
Assess extramedullary plasmacytomas	X[k]	Measurable sites every 4 weeks (if applicable) (for physical examination) and every 12 weeks (for radiologic examination) for subjects with a history of plasmacytomas or as clinically indicated for others								X[l]	

Abbreviations: COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for Research and Treatment of Cancer; EOT=End-of-Treatment; FFPE= formalin-fixed paraffin embedded; FLC=free light chain; FUP=Follow-up Phase; ICF=informed consent form; IV=intravenous; QIg=quantitative immunoglobulins; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetics; PD=progressive disease; PFS=progression-free survival; SAE=serious adverse event; sCR=stringent CR; SPEP=Serum M- protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis

Note: **Study drug** is defined as daratumumab and pomalidomide.

a) To occur within 7 days after discontinuation of all study treatment.

b) In the 90 (+3) days after the last dose of daratumumab for safety follow-up visits. For subjects who discontinue study treatment before PD, disease evaluations should continue to be performed at the frequency specified below until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent to study participation, or end of the study, whichever occurs first. Once PD is confirmed, subsequent disease evaluation time points are not required.

- Every 8-12 weeks (±3 days), at clinician's discretion: SPEP and 24-hour UPEP assessments, and serum calcium corrected for albumin
- Every 4 weeks (±3 days), or at clinician's discretion: physical examination of extramedullary plasmacytomas if applicable
- Every 12 weeks (±14 days), or at clinician's discretion: radiologic imaging of extramedullary plasmacytomas if applicable
- When CR is suspected or maintained: serum FLC, serum and urine immunofixation
- As clinically indicated: skeletal survey

- Evidence of clinical relapse will also be documented at the time at which it is first detected. After PD is determined, patient will be taken off study and no further study evaluations will be needed.
c) Blood pressure is to be measured at the following time points on Cycle 1 Days 1: immediately pre-administration, at the end of administration, 30 minutes post administration, 60 minutes post administration, and then hourly until 6 hours post administration. On Cycle 1 Day 8: immediately pre-administration, at the end of administration, 30 minutes post administration, 60 minutes post administration, and 120 minutes post administration. On Cycle 1 Day 15 onward: immediately pre-administration, at the end of administration, 15 minutes post administration. Infusion observation times and vital signs may be adjusted per PI discretion.
d) Pre-infusion medications to be given before all daratumumab infusions (if necessary, oral pre-infusion medications may be administered at the subject's home on the day of the infusion, provided they are given within 3 hours prior to the infusion)
e) Unless otherwise stated, all blood and urine samples must be obtained before administration of study treatment.
f) During Screening, to be performed within 10-14 days prior to dosing and then again within 24 hours prior to dosing. During the Treatment Phase, to be performed weekly during Cycle 1 and then monthly in subsequent cycles in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.
g) Results of these laboratory tests must be evaluated before each study treatment administration. At Cycle 1 Day 1, these tests do not need to be repeated if they have been performed within 7 days.
h) Samples must be sent to the clinical laboratory at MDACC.
i) Following the primary PFS analysis, efficacy assessments will be performed according to the standard of care for subjects without disease progression.
j) Bone marrow biopsy examination with NGF-based MRD testing at 6 months (+/- 2 weeks) from the start of maintenance then yearly as clinically indicated.
k) Should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging.
l) At 6 months after the subject's first dose, the timing of radiologic assessment of extramedullary plasmacytomas should follow the standard of care.
m) It is recommended that in addition to ABO and Rh blood typing, indirect antiglobulin test (also known as indirect Coombs test) be performed and that the subject carries a card with the blood antigen profile at all times during the study.
n) Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
o) Patients will be evaluated either in person or remotely via telemedicine or telephone. If patient is seen remotely via telemedicine or telephone physical exam, vital signs, and weight are not required..
p) **Hepatitis Tests:** - **HBV Serology:** All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. - **HBV DNA Tests:** Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study

treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV. Where required by local law, the results of HBV testing may be reported to the local health authorities.